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Dramatic synergistic effects between hydroquinone and resorcinol derivatives for the organocatalyzed reduction of dioxygen by diethylhydroxylamine†

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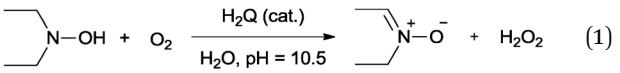
Raphaël Lebeuf, Véronique Nardello-Rataj and Jean-Marie Aubry*

Diethylhydroxylamine reduces dioxygen in the presence of catalytic amounts of hydroquinone. A great improvement is achieved by adding resorcinol derivatives as co-catalysts. Though the formation of heterodimers does not seem to be the sole cause of the synergy, such products constitute a new class of powerful organocatalysts for dioxygen scavenging.

In addition to being key biologically active compounds,[1,2] antioxidants are ubiquitous inhibitors to prevent the oxidative degradation of many end-use products such as polymers, lubricants, foods, cosmetics and fragrances.[3–5] Most of them act as radical chain breakers once the dioxygen has reacted with the substrate.[6] They constitute a class of primary antioxidants according to Ingold classification.[7] The so-called secondary antioxidants prevent oxidation through any other process except direct radical trapping. Dioxygen scavengers belong to this category as they provide anaerobic media by direct reduction of dioxygen. The main industrial application of such a system is the deoxygenation of boiler water, in order to prevent corrosion of metallic surfaces.[8] For this purpose, the catalytic system composed of diethylhydroxylamine and hydroquinone (**DEHA–H_2Q**) is one of the most effective[9] since hydroquinone rapidly reacts with dioxygen in aqueous basic solution.[10]



(1)

As H_2Q is potentially carcinogenic, we sought to boost its activity to reduce its concentration or replace it by a more efficient catalyst. Most of the substituents grafted onto hydroquinone lead to the depletion of the activity. However, with methoxy and chlorine substituents, the reactions run faster, albeit without improving the TON because of degradation of the catalysts.[11] A first approach to improve the catalytic system was to find more active polyphenols that led to the identification of gallic acid as a safer alternative to hydroquinone.[11,12] Alternatively, antioxidants are well-known to present synergistic effects in radical trapping chain transfer reactions, like the combination of 2,5-di-*tert*-butyl-3-methylphenol (BHT) with 2-*tert*-butyl-4-hydroxyanisole (BHA),[13] or tocopherol with ascorbic acid.[14] Such synergies between dioxygen scavengers have however, to the best of our knowledge, not been reported yet.

We first assessed the catalytic activity of the 3 dihydroxybenzene regioisomers (hydroquinone **1**, catechol **2** and resorcinol **3a**) alone or pairwise (Fig. 1). The concentration of dissolved dioxygen ($[O_2]_0 \approx 0.28$ mM) in a buffered alkaline solution ($[NaHCO_3]$ = 10 mM, $[Na_2CO_3]$ = 16 mM, pH = 10.1) containing a 3 fold excess of **DEHA** (0.84 mM) was monitored as a function of time thanks to a dioxygen electrode based on luminescence extinction, in the presence of different catalysts (total concentration = 16 μm). Hydroquinone **1** is a much better catalyst than catechol **2**, whereas resorcinol **3a** does not catalyze the reaction at all since the same conversion of O_2 is observed

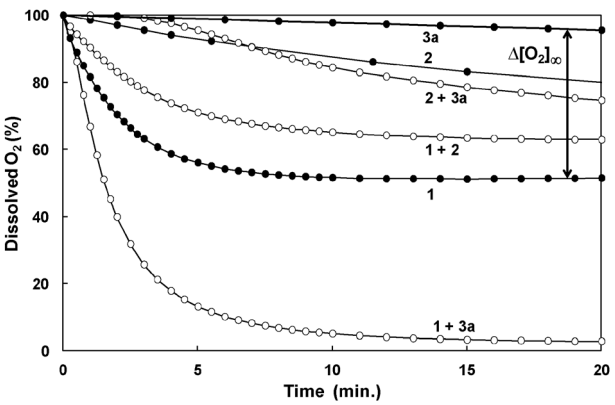


Fig. 1 Consumption of dissolved O_2 by DEHA as a function of time in the presence of hydroquinone **1**, catechol **2** and resorcinol **3a** alone (●) or pair wise in stoichiometric amounts (○). Conditions: $[O_2]_0$ = 0.28 mM, [DEHA] = 0.84 mM, [total catalyst] = 16 μM, pH = 10.1, T = 25 °C.

Université Lille Nord de France, Université Lille 1 and ENSCL, EA 4478 Chimie Moléculaire et Formulation, Cité Scientifique – BP 90108, 59652 Villeneuve d'Ascq Cedex, France. E-mail: jean-marie.aubry@univ-lille1.fr; Tel: +33 (0)320436364

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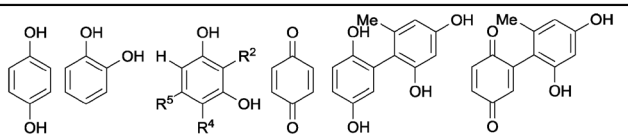
without catalyst. This slow disappearance of O_2 is due to the uncatalyzed reaction of DEHA with O_2.[15]

The combination of hydroquinone **1** with catechol **2** in a 1 : 1 ratio gives the expected curve between the ones obtained using the two components separately. However, its profile is closer to that of hydroquinone than to catechol, as it levels off after 10 minutes only. This behavior suggests that the two catalysts interact with each other. The mixture of catechol **2** and resorcinol **3a** shows a complicated synergistic effect since no reaction occurs at the beginning but, after a lag time of ≈5 min, the reaction starts and leads to higher O_2 consumption despite the half lower concentration of catechol and the lack of reactivity of resorcinol. A much more dramatic synergistic effect is observed for the mixture hydroquinone **1**–resorcinol **3a** since almost all dissolved oxygens disappear within 15 min (Fig. 1).

To further investigate this remarkable synergy, eleven resorcinol derivatives **3a–k** were screened to determine the influence of the position and the electronic effects of their substituents on the synergy with hydroquinone **1**, and to further improve the catalytic system. Table 1 lists, for all the investigated systems, the maximum turnover frequency (TOF_{max}) reached after a few seconds of reaction and the maximum percentage of O_2 consumed, conv. = $\Delta[O_2]_\infty$, once the catalyst is completely degraded (see Fig. 1). To facilitate comparisons, the turnover numbers (TON) have also been reported. Very low concentrations of hydroquinone and of co-catalysts were used (1 μM for each of them) to let residual dioxygen, thus allowing comparison of the catalytic systems.

None of the resorcinol derivatives exhibit catalytic activity when used alone at 1 μM concentrations, except pyrogallol **3b** which gives 29% of conversion (see ESI†). Comparing the activity of the various substituted co-catalysts **3b–k** with that of resorcinol **3a** itself (entry 2) shows that a third OH group grafted onto the resorcinol core (pyrogallol **3b** and phloroglucinol **3c**) is detrimental to the synergistic effect probably because it increases their susceptibility to degradation (entries 3 and 4). The presence of a methyl group in positions 2 and 4 has no effects whereas in position 5 (orcinol, **3f**) the synergy is greatly improved, both in terms of the reaction rate and conversion (entries 5–7). We then studied in more detail the influence of various R_5 substituents bound to this crucial position. The electron-donating groups OCH_3, COO^- and C_6H_5 have also a beneficial effect but they fail to perform better than CH_3 (entries 8, 11 and 12). The electron-withdrawing group COOEt suppresses, almost completely, the synergistic effect (entry 10) whereas Cl induces the same effect as H (entry 9), confirming that no clear correlation can be established between the Hammet constants of the substituents and the reaction rate. Hence, substitution at the *meta* position of the resorcinol pattern with an electron-donating substituent other than an OH group is highly beneficial for the catalytic activity.

Table 1 Consumption of dioxygen dissolved in water by DEHA in the presence of polyphenolic catalysts and co-catalysts. Conditions: $[O_2]_0$ = 0.28 μM, [DEHA] = 0.84 μM, [catalyst] = 1 μM, [co-catalyst] = 1 μM, pH = 10.1, T = 25 °C



1 2 3 4 5 6

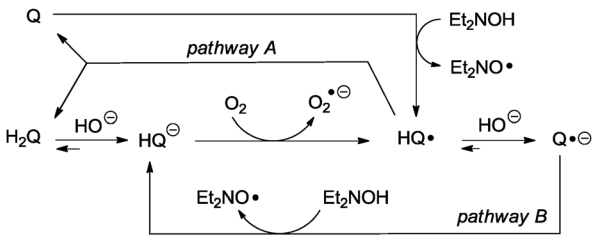
Entry	Cat.	Co-cat.	R^2	R^4	R^5	Conv. (%)	TOF_{max}[a] (min^{-1})	TON[a]
1	1	**1**	—	—	—	18	6	50
2	1	**3a**	H	H	H	57	14	160
3	1	**3b**	OH	H	H	24	5	67
4	1	**3c**	H	H	OH	27	7	76
5	1	**3d**	Me	H	H	59	17	165
6	1	**3e**	H	Me	H	56	18	157
7	1	**3f**	H	H	Me	89	27	249
8	1	**3g**	H	H	OMe	81	16	227
9	1	**3h**	H	H	Cl	58	15	162
10	1	**3i**	H	H	CO_2Et	24	4	67
11	1	**3j**	H	H	CO_2H	85	16	238
12	1	**3k**	H	H	Ph	77	21	216
13	4	**3f**	H	H	Me	90	31	252
14	5	—	—	—	—	88	15	246
15	6	—	—	—	—	86	17	241

[a] Relative to catalysts only.

The mechanism of the binary **DEHA–H_2Q** catalytic system (eqn (1)) has already been discussed in detail.[11] The rate limiting step is believed to be the regeneration of hydroquinone **H_2Q** or its conjugated base **HQ^-**, either through disproportionation of the semiquinone radical **$HQ^\bullet$** into **H_2Q** and benzoquinone **Q** (Scheme 1, pathway A), or its direct reduction by **DEHA** (Scheme 1, pathway B).

According to the mechanism of pathway A and the literature,[16] **Q** is reduced by **DEHA** to **$HQ^\bullet$**. Therefore, **Q** can also be used as a catalyst instead of **H_2Q**. Indeed, the experiment carried out using benzoquinone **4** as a catalyst and orcinol **3f** as a co-catalyst shows a similar synergistic effect to that carried out using hydroquinone **1** with **3f** (compare Table 1, entries 7 and 13, and Fig. 2).

Although this result does not prove the formation of benzoquinone during the catalytic cycle, the possibility of *in situ* formation of a more active catalyst from benzoquinone was considered. This hypothesis follows the work of Kurechi's group, who claimed that heterodimer by-products obtained from a mixture of two phenolic antioxidants might be responsible for their synergy in radical chain trapping processes.[17] For instance, they show that the heterodimer of the couple BHA–BHT exhibits a higher antioxidant activity than the single compounds.[13] In an attempt to form an eventual heterodimer, concentrated benzoquinone **4** (0.2 M) and orcinol **3f** (0.2 M)



Scheme 1 Proposed mechanisms for the reduction of dioxygen by the catalytic system **DEHA–H_2Q**.

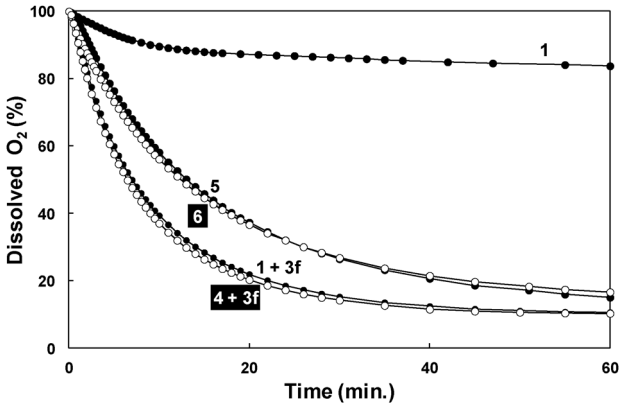
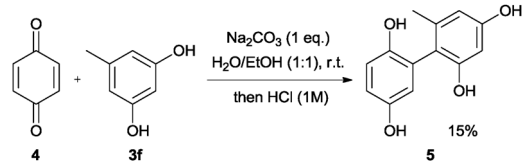


Fig. 2 Dioxygen reduction in water as a function of time for hydroquinone **1** (1 μM), hydroquinone **1** + orcinol **3f** (1 + 1 μM), benzoquinone **4** + orcinol **3f** (1 + 1 μM), heterodimer **5** (1 μM), and heterodimer **6** (1 μM). Conditions: [DEHA] = 0.84 mM, $[O_2]_0$ = 0.28 mM, pH = 10.1, T = 25 °C.



Scheme 2 Condensation reaction between benzoquinone and orcinol.

were mixed together in basic aqueous media under argon. After a few minutes, benzoquinone was completely consumed and the heterodimer **5** was isolated with 15% yield besides polymeric by-products (Scheme 2).

No redox process is required for this condensation that may involve successively 1,4-addition of **3b** to **4** and two tautomerizations of the adduct (see ESI†). Surprisingly, this heterodimer has not been reported so far in the literature although similar condensation products have been obtained by reaction of resorcinol **3a** on benzoquinone[18] **4** or acylbenzoquinone[19] under acidic or basic conditions. Musso *et al.* also reported the synthesis of a heterodimer with 21% yield by reacting resorcinol **3a** with hydroxyquinone **1** in aerobic basic solution[20] but the antioxidant properties of such compounds have not been investigated.

As shown in Fig. 2, the heterodimers **5** and **6** are clearly more stable than their corresponding binary catalytic systems **1** + **3f** and **4a** + **3f** since they lead to similar O_2 conversions although the TOFs are about two times smaller (15 and 17 min^{-1} *vs.* 27 and 31 min^{-1}, entries 14 and 15 *vs.* 7 and 13). These results indicate that the synergy is not only due to the formation of the heterodimers **5** or **6**, even if their formation and participation in the catalytic process cannot be ruled out. An alternative to the establishment of a covalent bond between resorcinol **3a** and hydroquinone **1** could be the formation of a charge transfer complex (CTC). Indeed, a CTC between benzoquinone **4** and resorcinol **3a** has been described in a neutral aqueous environment,[21,22] and may well also form in basic medium. It would change the redox potential of each compound and could accelerate the regeneration of $\mathbf{HQ}^-$ facilitating the transfer of a hydrogen atom from resorcinol or **DEHA** to the $\mathbf{Q}^{\bullet -}$ radical. The validity of this assumption is under consideration.

In conclusion, the binary catalytic systems based on hydroquinone + resorcinol derivatives exhibit dramatic synergistic activities for dioxygen reduction by **DEHA**. The likely formation of a heterodimer as proposed in the literature for other antioxidant synergies does not seem to be the sole explanation herein, as revealed by the study of one of them. However, the effectiveness of these heterodimers as oxygen scavengers will encourage us to pursue the study of this new class of organocatalysts to define their mode of action, as well as their efficiency as catalysts and/or antioxidants in other processes involving radical chain transfer reactions.

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